Council for Responsible Nutrition
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Re: Comments on:
1. Proposition 65 Regulatory Update Project – Regulatory Concepts for Exposure to Human and Plant Nutrients in a Human Food
2. Draft Initial Statement of Reasons - Title 27, California Code of Regulations: Proposed New Sections 25506 and 25507 Exposures to Human and Plant Nutrients in a Food

Dear Ms. Kammerer:

These comments are filed on behalf of the Council for Responsible Nutrition (CRN), the leading trade association representing dietary supplement manufacturers and ingredient suppliers. CRN companies produce a large portion of the dietary supplements marketed in the United States and globally. Our member companies manufacture popular national brands as well as the store brands marketed by major supermarkets, drug store and discount chains, as well as through natural food stores and mainstream direct selling companies.

We continue to believe, as stated in our previous comment on May 2, 2008, that this project is not needed, as illustrated by the original position that OEHHA took on retinol. Up to now, retinol is the only chemical listed as a DART or carcinogen and that is also a beneficial nutrient. When retinol listed, OEHHA made an appropriate decision through a case-by-case approach, similar to what is being proposed now. Although no general rules were in place at that time to guide the OEHHA decision on retinol, it is worthwhile to examine that decision to identify the *de facto* rules that were applied. In that instance, the original decision on retinol was made through a case-by-case approach that employed a labeling threshold of any excess above the intake that was later identified by the U.S. Food and Nutrition Board (FNB) as the Tolerable Upper Intake Level (UL). No other rules applied after retinol was identified as a DART when levels were sufficiently excessive.

If OEHHA currently considers other beneficial nutrients to warrant possible listing as a DART or carcinogen, it should give public notice about which those are so that stakeholders can prepare substantive comments with full information about the chemicals

under consideration rather than dealing in hypotheticals. Alternatively, OEHHA could dismiss this current rulemaking and then, at the time of listing, a case-by-case approach could be employed in the absence of any generalized rulemaking, as it did with retinol. However, assuming that OEHHA has rejected the possibility of terminating this rulemaking proceeding, CRN will continue by providing constructive suggestions for improvements to the proposal.

Regarding the current draft, the OEHHA Draft-Proposed new Sections 25506 and 25507 (released on 11/03/08) represents significant improvement in the general approach over the Draft Regulatory Concept released earlier this year in that the new draft specifies a chemical-by-chemical decision process, rather than a uniform percentage or some other type of standard. CRN applauds the agency's recognition that nutrients are vastly different in their metabolism and usage by the human body, and thus, a flat, arbitrary, across-the-board level is neither workable nor useful. A flexible approach that accounts for nutrient differences, as now proposed by OEHHA, has much more likelihood of addressing necessary and recommended levels of these beneficial nutrients.

Unfortunately, the draft Sections 25506 and 25507 and the draft statement of reasons intended to justify and explain them still contains significant ambiguities, misquotes, and misunderstandings. Our principal concerns are listed and described below. Moreover, Sections 25506 and 25507 are incomplete in a manner that prevents any firm conclusion about whether the changes to a case-by-case approach to evaluation of beneficial nutrients truly represent a significant step in the right direction. Specifically, paragraphs b. in both 25506 and 25507 indicate that a "Maximum Daily Exposure from a Food (micrograms per day)" will need to be identified. Neither section nor any supporting documents indicates the method and standard for establishing these values.

GENERAL CONCERNS

<u>"Naturally occurring" exemption issues in both Sections 25506 and 25507</u>. As this exception would likely be applied to dietary supplements, it is hard to see how it would have any benefit at all. The required burden of proof for a dietary supplement to meet this threshold seems nearly impossible. That is, a chemical is considered to be naturally occurring only if it can be shown not to have been added. For chemicals that are nutrients and that occur naturally at a variety of concentrations in foods, it is logically impossible to show that any specific level did not result from human activity—no matter how long in the past that activity might have occurred.

This becomes more problematic for beneficial nutrients that may be included in dietary supplements because they are by definition, products that are "intended to supplement the diet." It appears that *any* chemical (including beneficial nutrients) known to be added to a product, or even to one's daily regimen, in order to supplement the diet, such as in fortified foods and dietary supplements, may not qualify for "naturally occurring." On the other hand, if the chemical might have occurred naturally at the concentration in question or might have resulted from some inadvertent but unknown human activity, how

would OEHHA tell the difference if the concentration were in the range that can occur naturally? For any chemical that was included in food because it is a plant nutrient (and the majority of these are also human nutrients), how would OEHHA rule on whether the amount is necessary for healthy plant development?

1. Lack of methods and standards for identification of quantitative "Maximum Daily Exposure from a Food (micrograms per day)"

As a separate issue, the decision to establish the Maximum Daily Exposure Level from a food (MDEL) on a case-by-case basis is a significant step in the right direction. By itself, however, this approach is not sufficient to assure scientifically justified outcomes. Case-by case decisions can be just as arbitrary as the earlier 20% of Upper Level (UL) method, if there are no criteria or guidelines for the process. The discipline of risk assessment for nutrients has developed and evolved in the last 10-15 years to include widespread recognition by health and regulatory authorities that it must differ in major ways from the risk assessment for non-nutrient substances. The UL method, originally developed by the FNB, has been adopted by the European Commission scientific and regulatory bodies, the U.K. Food Standards Agency, the World Health Organization in a joint report with the UN Food and Agriculture Organization, and the Codex Alimentarius. The accounting for uncertainty in the UL method is fundamentally different from that under Proposition 65. Fortunately, early on OEHHA made the decision for vitamin A (as retinol and retinyl esters) not to follow the 1000X factor specified in Proposition 65 because it would put warnings on products unless they were limited to clearly inadequate to useless amounts. In the current redrafted document for Beneficial Nutrients, no discussion is provided on whether the new case-by-case approach will allow similar digressions from the 1000X factor for a similar justification. Clarity is needed on this issue before OEHHA moves ahead with further development of Sections 25506 and 25507.

2. Confusion of "no observable effect level" and Tolerable Upper Intake Level (UL)

In the second paragraph on Necessity for Section 25506 OEHHA provides a hypothetical example and gives the correct qualifying definition for the UL but inappropriately describes it as equivalent to a "maximum no-adverse-effect-level." These terms are NOT equivalent because, using preformed vitamin A (retinol) intake by women of reproductive age as the example, the FNB identified a No Observed Adverse Effect Level (NOAEL) for birth defects and calculated the UL by dividing by an Uncertainty Factor (UF) of 1.5. With retinol for other adults, the FNB identified a Lowest Observed Adverse Effect Level (LOAEL) for liver pathology and divided by a UF of 5. Clearly, neither the NOAEL nor the LOAEL is equivalent to a "maximum no observable effect level." That is, the UL is not a threshold of any kind. These points need substantial revision in the new draft by OEHHA.

3. Extrapolation from health effects not covered by Proposition 65 to DART or carcinogenic effects

In discussion of the utility of FNB UL values in decision making under Proposition 65, OEHHA has correctly recognized that many UL values are based on toxicities other than DART or carcinogenic effects. The OEHHA document correctly concludes that these UL values are not directly useful in setting MDEF values for foods, but nonetheless makes an unsupported assertion that these other effects "can inform their development." CRN does not agree, and recommends that OEHHA either give an adequate explanation with examples, or withdraw this statement and any possible plans to use this approach.

SPECIFIC CONCERNS FOR STATEMENT OF REASONS

1. Section 25506--Statement of Purpose

    a. The second paragraph incorrectly uses the term "Recommended Daily Allowance" as having come from the U.S. Food and Nutrition Board (FNB). The correct term is "Recommended Dietary Allowances," which is commonly given the acronym RDA.

    b. For several nutrients, the FNB set an "Acceptable Intake" (AI) instead of an RDA because they could not find the appropriate quantitative basis for identifying an Estimated Average Requirement (EAR) and calculating an RDA (EAR + 2SD). How would OEHHA handle a nutrient with an AI, but not an RDA?

2. Section 25507—discussion of Necessity

    a. It is not clear how the levels would be identified that OEHHA considers appropriate (that is, not requiring warning labels) as a result of supplementing the plant's nutrient needs. Would this be the minimum level to prevent deficiency of that nutrient in the plant? Would a level be permitted that is generally considered to provide the minimum plus a reasonable margin to assure that the plant would not be deficient?

    b. Would the exemption level be related to the impact of that level on the plant's health, or to its "presence due to use to promote plant growth?" Along this line, would "growth" be considered to include any other desirable aspect of the plant's health, such as fruit or seed production?

<u>CRN's Recommendations and Rationale</u>:
We recommend the following modifications of the draft before any further actions are taken on it:

Recommendation:

Our primary recommendation is to discontinue the development of this new regulatory policy. If this cannot be done, we recommend criteria and standards that are consistent with the action taken on retinol many years ago.

For any nutrient, should it become listed as a DART or carcinogen:

1. A nutrient will qualify as "Beneficial Nutrient" and will be exempted from constituting an exposure if the nutrient and the amount of nutrient in the product meets the following criteria:
    a. The nutrient has a
        i. Recommended Dietary Allowance (RDA), e.g.. retinol, or
        ii. Acceptable Intake (AI), e.g., vitamin D, established by the US Food and Nutrition Board (FNB), or
        iii. is recognized in the FNB documents on Dietary Reference Intakes as having nutritive effects, e.g., lutein, but lacks sufficient data to set an RDA or an AI, or
        iv. the nutrient is the subject of a health claim approved by the US Food and Drug Administration, e.g., dietary fiber; **and**
    b. The amount of the nutrient in the product (based on dosage instructions or serving amounts according to package labeling) does not exceed:
        i. the Tolerable Upper Intake Level (UL) established by the FNB (OEHHA was prescient and set its retinol warning threshold at 10,000 IU, the amount that the U.S. Food and Nutrition Board later set as the UL), or
        ii. for those low toxicity nutrients for which FNB found no toxicological basis for a UL, the intake would be less than the Guidance Level established by the United Kingdom Expert Committee on Vitamins and Minerals (EVM), or
        iii. the equivalent of Highest Observe Intake (HOI) as defined in a report by the World Health Organization/Food and Agriculture organization (WHO/FAO), or its equivalent in the peer reviewed literature.

2. A nutrient will qualify as a "Plant Nutrient" and be exempted:
    a. Under criteria recognized by plant nutrition expert bodies that are analogous to the human nutrition criteria in 1.a., above; **and**
    b. The amount of the nutrient in the product meets the criteria in 1.b., above.

Rationale:

The criteria in 1.a. and 2.a., above, establish the nutrient as a Beneficial Nutrient or a Plant Nutrient, respectively.

The criteria in 1.b, and 2.b., above, establish that the level of the nutrient is considered safe by appropriate experts, and thus any warnings required under Proposition 65 would be counter productive to the availability and consumption of beneficial foods that promote the health of consumers.

Regarding the criteria in 1.b. and 2.b., it should be recognized that the UL value is not a threshold for toxicity, but includes a substantial margin of safety. That is, the UL is a level below any known threshold that is deemed by the authorities as providing a sufficient margin of safety. This margin of safety is robust enough that the cumulative impact of consumption of multiple products subject to the provisions of Proposition 65 would create little likelihood of producing total intakes that exceed the UL. Note that the FNB set a retinol (preformed vitamin A) UL of 10,000 IU (3,000 µg). This value was derived from the data of Rothman et al. (1995) that claimed a small increase in certain birth defects when the maternal supplementation was at a media of 21,700 IU. The lowest value was "more than 15,000 IU" and this value was judged to be the No Observed Adverse Effect Level and an uncertainty factor of 1.5 was selected to calculate the UL. Clearly, the FNB UL for retinol carries a substantial margin of safety and 10,000 IU is nowhere near a biological threshold for DART effects.

In strict application of the UL method, the FNB chose not to identify a UL for nutrients without any established toxicity. If such a nutrient should be listed under Proposition 65, the Guidance Level from the EVM or the HOI as defined by the WHO/FAO, or its equivalent in the peer reviewed literature, could be used to identify the level that should be exempted as a Beneficial or Plant Nutrient.

Thank you for the opportunity to comment.

Sincerely yours,

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